# PRODUCT MONOGRAPH

## [Pr] EPIRUBICIN HYDROCHLORIDE FOR INJECTION

50 mg / vial

Sterile

**Antineoplastic Agent**

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## PART I: HEALTH PROFESSIONAL INFORMATION

### CAUTION

EPIRUBICIN HYDROCHLORIDE FOR INJECTION IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. IRREVERSIBLE CARDIAC TOXICITY MAY OCCUR AS THE CUMULATIVE DOSE APPROACHES 1000 mg/m$^2$. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED MEDIASTINAL RADIOTHERAPY, OTHER ANTHRACYCLINE OR ANTHRACENE THERAPY, WITH PRE-EXISTING CARDIAC DISEASE, OR RECEIVED PRIOR EPIRUBICIN CUMULATIVE DOSES EXCEEDING 650 mg/m$^2$.

SECONDARY ACUTE MYELOID LEUKEMIA (AML) WITH OR WITHOUT A PRELEUKEMIC PHASE (MYELODYSPLASTIC SYNDROME OR MDS) HAS BEEN REPORTED IN PATIENTS TREATED WITH EPIRUBICIN-CONTAINING REGIMENS. THE CUMULATIVE RISK OF DEVELOPING TREATMENT-RELATED AML/MDS IN 7110 PATIENTS WITH EARLY BREAST CANCER WHO RECEIVED ADJUVANT TREATMENT WITH EPIRUBICIN-CONTAINING REGIMENS WAS ESTIMATED AS 0.27% AT 3 YEARS, 0.46% AT 5 YEARS, AND 0.55% AT 8 YEARS.

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Non-medicinal Ingredients |
|---|---|---|
| Intravenous | lyophilized powder for injection / 50 mg vials | Not Applicable.<br>*For a complete listing see Dosage Forms, Composition and Packaging section* |

## INDICATIONS AND CLINICAL USE

Epirubicin Hydrochloride for Injection has been used successfully as a single agent and in combination with other chemotherapeutic agents to produce regression in a variety of tumour types such as lymphoma, lung, cancer of the breast, ovary and stomach.

Epirubicin Hydrochloride for Injection is recommended for the treatment of metastatic breast cancer.

Epirubicin Hydrochloride for Injection may also be used as a component in the adjuvant treatment of early stage breast cancer for pre- and peri- menopausal women.

Epirubicin Hydrochloride for Injection is also recommended in small cell lung cancer (both limited and extensive disease) advanced non-small cell lung cancer, non-Hodgkin's lymphoma, Hodgkin's disease, Stage III and IV (FIGO) ovarian carcinoma and metastatic and locally unresectable gastric carcinoma.

In addition, several other solid tumours have shown responsiveness to Epirubicin Hydrochloride for Injection but data are not yet sufficient to justify specific recommendations.

## CONTRAINDICATIONS

• Hypersensitivity to epirubicin or any other component of the product, or other anthracyclines or anthracenediones such as doxorubicin hydrochloride, daunorubicin hydrochloride, mitoxantrone or mitomycin C.
• marked persistent myelosuppression induced by prior treatment with other antitumour agents or by radiotherapy
• severe hepatic impairment
• severe myocardial insufficiency
• recent myocardial infarction
• severe arrhythmias
• history of severe cardiac disease
• previous treatments with maximum cumulative doses of epirubicin and/or other anthracyclines and anthracenediones (see WARNINGS AND PRECAUTIONS).

## WARNINGS AND PRECAUTIONS

### Cardiac Function:

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.

**Early (i.e., Acute) Events.** Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually

predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for the discontinuation of epirubicin treatment.

**Late (i.e., Delayed) Events.** Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin or within 2 to 3 months after treatment termination, but later events several months to years after completion of treatment have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of Epirubicin Hydrochloride for Injection therapy.

Given the risk of cardiomyopathy, a cumulative dose of 900 to 1000 mg/m$^2$ epirubicin should generally not be exceeded. Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of other drugs with the ability to suppress cardiac contractility. Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. While cardiotoxicity with epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present, it may be more likely to occur at lower cumulative doses in patients with these risk factors.

Available evidence appears to indicate that cardiotoxicity is cumulative across members of the anthracycline and anthracene class of drugs. Patients who have previously received other anthracyclines and anthracenes are at particular risk for possible cardiotoxic effects of Epirubicin Hydrochloride for Injection at a lower total dose than previously untreated patients and, therefore, should be carefully monitored. The total dose of Epirubicin Hydrochloride for Injection administered to a patient should take into account: prior or concomitant therapy with related compounds such as doxorubicin and daunorubicin or anthracene derivatives; and/or radiotherapy to the mediastinal area.

Anthracycline-induced cardiac failure is often resistant to currently available therapeutic and physical measures used for the treatment of cardiac failure. Early clinical diagnosis of drug-

induced heart failure is essential. Treatment measures include digitalis, diuretics, peripheral vasodilators, low salt diet, and bed rest. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. An EKG, echocardiogram or radionuclide angiography (MUGA) performed at baseline and prior to each dose or course after a cumulative dose of 650 mg/m$^2$ is suggested. Transient EKG changes consisting of T-wave flattening, S-T depression and arrhythmias occurring up to two weeks after a dose or course of Epirubicin Hydrochloride for Injection are presently not considered indications for suspension of Epirubicin Hydrochloride for Injection therapy.

Epirubicin Hydrochloride for Injection cardiomyopathy has been reported to be associated with a reduction of the ejection fraction as determined by radionuclide scan or echocardiography. None of these tests have yet consistently identified those individual patients that are approaching their maximally tolerated cumulative dose of Epirubicin Hydrochloride for Injection. If test results indicate a change in cardiac status associated with Epirubicin Hydrochloride for Injection therapy, the benefit of continued therapy must be carefully weighed against the risk of producing irreversible cardiac damage.

**Hematologic Toxicity:**

Careful haematologic monitoring is required since bone marrow depression, primarily of leukocytes may occur. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell counts (WBC).

With the recommended dosage schedule (see DOSAGE AND ADMINISTRATION) leukopenia is transient, reaching its nadir 10-14 days after treatment, with recovery usually occurring by the 21$^{st}$ day. White blood cell counts as low as 1000/mm$^3$ are to be expected during treatment with Epirubicin Hydrochloride for Injection.

Red blood cell and platelet levels should be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or delay or suspension of Epirubicin Hydrochloride for Injection therapy. Persistent myelosuppression may result in infection or hemorrhage.

Epirubicin Hydrochloride for Injection may potentiate the toxicity of other anticancer therapies as well as radiation induced toxicity to the myocardium, mucosa and skin. Patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia and generalized infections) of prior cytotoxic treatment before beginning treatment with Epirubicin Hydrochloride for Injection.

While treatment with high doses of epirubicin (e.g., $\geq$ 90 mg/m$^2$ every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m$^2$ every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of the drug does require special attention for possible clinical complications due to profound myelosuppression.

**Liver Function:**

Epirubicin is extensively metabolized by the liver and its major route of elimination is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients (see DOSAGE AND ADMINISTRATION). Patients with severe hepatic impairment should not receive epirubicin (see CONTRAINDICATIONS).

**Renal Function:**

Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in patients with serum creatinine > 5 mg/dL (see DOSAGE AND ADMINISTRATION).

**Secondary Leukemia:**

The occurrence of secondary acute myeloid leukemia (AML) with or without a preleukemic phase (myelodysplastic syndrome or MDS) has been reported in patients treated with epirubicin-containing regimens. Such cases could have a short (1-3 years) latency period (see below and in Table 2 under ADVERSE REACTIONS).

The quantified risk of developing acute myeloid leukemia (AML), including myelodysplastic syndrome (MDS), following epirubicin or epirubicin-containing therapy, has been estimated by analyzing data collected prospectively from 19 randomized trials for the adjuvant treatment of early breast cancer, that were either company-sponsored or conducted by independent institutions (including the National Institute of Canada's MA.5 trial, see CLINICAL TRIALS, Early Stage Breast Cancer Studies). As of 31 December 2001, 28 (0.39%) of the 7,110 evaluable patients treated with epirubicin, had presented with either AML or MDS. An additional 4 patients were diagnosed with other types of leukemia: 3 with acute lymphoblastic leukemia (ALL), and 1 with chronic lymphocytic leukemia (CLL). The time elapsed from the start of adjuvant treatment to the diagnosis of AML/MDS ranged from 8 to 126 months, with a median of 33 months. Of the 23 cases of AML/MDS for whom cytogenetic information was available, in 12 there was evidence of balanced chromosome translocations, and in 7 these translocations involved chromosome 11 or 21. Therapy-induced leukemia secondary to topoisomerase inhibitors generally has a short induction period (6 months to 5 years) and is known to be associated with translocations involving chromosome 11 or 21.

In this most recent analysis, the cumulative risk of developing AML/MDS in the 7,110 patients treated with epirubicin was 0.27% (95% confidence interval 0.14%, 0.40%) at 3 years, 0.46% (95% confidence interval 0.28%, 0.65%) at 5 years, and 0.55% (95% confidence interval, 0.33%, 0.78%) at 8 years. AML/MDS rates increased with epirubicin dose per cycle, and cumulative dose. For instance, in the MA.5 trial, in patients that received intensive doses of epirubicin (120 mg/m$^2$), the incidence of AML/MDS was 1.1% at 5 years with no additional cases observed during the second 5 years (years 6-10) of follow-up.

Since the completion of these analyses, in the period up to and including September 2003, further spontaneous, literature and study reports of AML/MDS have been received.

In addition, in 10 trials for the treatment of advanced breast cancer (3061 patients, follow-up until March 1999), two cases of AML occurred. However, due to the small number of cases and the limited follow-up as a result of the natural history of advanced breast cancer in these patients, risk estimates could not be made for this patient population.

**General:**

Epirubicin Hydrochloride for Injection must not be administered by intramuscular or subcutaneous injection.

Severe local tissue necrosis can occur if Epirubicin Hydrochloride for Injection is extravasated during intravenous administration. Extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle (see DOSAGE AND ADMINISTRATION). If signs or symptoms of extravasation occur the injection or infusion should be terminated immediately and restarted in another vein.

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of epirubicin.

Epirubicin Hydrochloride for Injection is mutagenic, clastogenic, and carcinogenic in animals and has been associated with an increased risk of secondary leukemia (AML) in clinical trials of adjuvant treatment of breast cancer (see ADVERSE REACTIONS). In addition, epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should use effective contraceptive methods.

Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

Epirubicin Hydrochloride for Injection imparts a red colouration to the urine for 1 or 2 days after administration. Patients should be advised to expect this during active therapy.

**Usage in Pregnancy:**

There is no conclusive information about epirubicin adversely affecting human fertility, or causing teratogenesis; however, at high doses Epirubicin Hydrochloride for Injection is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no studies in pregnant women. Therefore, women of childbearing potential should be advised to avoid pregnancy.

Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If Epirubicin Hydrochloride for Injection is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be informed of the potential hazard to the fetus. Mothers should be advised not to breast-feed while undergoing chemotherapy with Epirubicin Hydrochloride for Injection.

**Monitoring and Laboratory Tests:**

Initial treatment with Epirubicin Hydrochloride for Injection requires close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, Epirubicin Hydrochloride for Injection may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The physician should monitor the patient's serum chemistry and blood uric acid level and be prepared to institute appropriate measures that might be necessary to control this problem. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Epirubicin Hydrochloride for Injection is not an anti-microbial agent.

**Information to be given to the patient:**

Patients should be counseled about the known adverse effects that they could experience during chemotherapy with Epirubicin Hydrochloride for Injection, including cardiotoxicity, myleosuppression and risk of infection, thrombocytopenia, anemia, nausea, vomiting, and stomatitis.

Physicians should also clearly lay out early on the risks and benefits of the various chemotherapeutic options available, thus enabling the patient to make an informed treatment choice. Patients should be aware that higher dose regimens may have a greater toxicity that includes secondary leukemia. Wherever possible, the physician should discuss the information presented in the 'CONSUMER INFORMATION' section.

## ADVERSE REACTIONS

Dose limiting toxicities are myelosuppression and cardiotoxicity (see WARNINGS AND PRECAUTIONS). Other reactions reported are:

**Cutaneous -** Reversible partial or complete alopecia occurs in most patients. Alopecia and lack of beard growth in males are usually reversible. Recall of skin reaction associated with prior radiotherapy may occur with Epirubicin Hydrochloride for Injection administration. Local toxicity, rash/itch and skin changes may also occur.

**Gastrointestinal -** Acute nausea and vomiting occurs frequently in most patients. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) has been reported to occur 5-10 days after administration. This may lead to ulceration and represents a site of origin for severe infections. Diarrhea has been reported. Most patients recover from this adverse event by the third week of therapy.

**Local -** Severe cellulitis, vesication, local pain and tissue necrosis can occur if Epirubicin Hydrochloride for Injection is extravasated during administration (see DOSAGE AND ADMINISTRATION). Erythematous streaking and/or transient urticaria along the vein proximal to the site of administration may occur. Venous sclerosis may result from injection into small veins or repeated injection into the same vein. Following the recommended administration

procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see SPECIAL HANDLING INSTRUCTIONS).

**Hematological -** A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) are the predominant manifestations of epirubicin bone marrow/haematologic toxicity and represents the acute dose-limiting toxicity of this drug. Leukopenia and neutropenia are usually more severe after administration of high-dose regimens; under these conditions appropriate bone marrow support (eg. peripheral blood progenitor cells and/or colony-stimulating factors) may be required. Thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

**Secondary Leukemia:** see WARNINGS AND PRECAUTIONS.

**Body as a Whole** - Phlebitis, fever and malaise/asthenia have been reported following administration of Epirubicin Hydrochloride for Injection.

Drug-related adverse events also occurred in the following systems:

**Endocrine –** amenorrhea and hot flashes

**Cardiovascular** – asymptomatic drops in left ventricular ejection fraction and congestive heart failure

**Ocular** – conjunctivitis, keratitis

**Other** - infection, acute lymphocytic leukemia, acute myelogenous leukemia

**Adverse Reactions in Early Breast Cancer Adjuvant Treatment:**

*On-Study Events*
Integrated safety data are available from two studies (Studies MA.5 and GFEA-05 (FASG-05), see CLINICAL TRIALS, Early Stage Breast Cancer Studies) evaluating epirubicin-containing combination regimens in patients with early breast cancer. Of the 1260 patients treated in these studies, 620 patients received the higher-dose epirubicin regimen (FEC-100/CEF-120), 280 patients received the lower-dose epirubicin regimen (FEC-50), and 360 patients received CMF. Serotonin-specific anti-emetic therapy and colony-stimulating factors were not used in these trials. Clinically relevant acute adverse events are summarized in Table 1.

**Table 1. Clinically Relevant Acute Adverse Events in Patients with Early Breast Cancer**

| Event | % of Patients | | | | | |
|---|---|---|---|---|---|---|
| | FEC-100/CEF-120 (N = 620) | | FEC-50 (N = 280) | | CMF (N = 360) | |
| | Grades 1-4 | Grades 3/4 | Grades 1-4 | Grades 3/4 | Grades 1-4 | Grades 3/4 |
| **Haematologic** | | | | | | |
| Leukopenia | 80.3 | 58.6 | 49.6 | 1.5 | 98.1 | 60.3 |
| Neutropenia | 80.3 | 67.2 | 53.9 | 10.5 | 95.8 | 78.1 |
| Anemia | 72.2 | 5.8 | 12.9 | 0 | 70.9 | 0.9 |
| Thrombocytopenia | 48.8 | 5.4 | 4.6 | 0 | 51.4 | 3.6 |
| **Endocrine** | | | | | | |
| Amenorrhea | 71.8 | 0 | 69.3 | 0 | 67.7 | 0 |
| Hot Flashes | 38.9 | 4.0 | 5.4 | 0 | 69.1 | 6.4 |
| **Body as a Whole** | | | | | | |
| Lethargy | 45.8 | 1.9 | 1.1 | 0 | 72.7 | 0.3 |
| Fever | 5.2 | 0 | 1.4 | 0 | 4.5 | 0 |
| **Gastrointestinal** | | | | | | |
| Nausea/vomiting | 92.4 | 25.0 | 83.2 | 22.1 | 85.0 | 6.4 |
| Mucositis | 58.5 | 8.9 | 9.3 | 0 | 52.9 | 1.9 |
| Diarrhea | 24.8 | 0.8 | 7.1 | 0 | 50.7 | 2.8 |
| Anorexia | 2.9 | 0 | 1.8 | 0 | 5.8 | 0.3 |
| **Infection** | | | | | | |
| Infection | 21.5 | 1.6 | 15.0 | 0 | 25.9 | 0.6 |
| Febrile neutropenia | NA | 6.1 | 0 | 0 | NA | 1.1 |
| **Ocular** | | | | | | |
| Conjunctivitis/keratitis | 14.8 | 0 | 1.1 | 0 | 38.4 | 0 |
| **Skin** | | | | | | |
| Alopecia | 95.5 | 56.6 | 69.6 | 19.3 | 84.4 | 6.7 |
| Local toxicity | 19.5 | 0.3 | 2.5 | 0.4 | 8.1 | 0 |
| Rash/itch | 8.9 | 0.3 | 1.4 | 0 | 14.2 | 0 |
| Skin changes | 4.7 | 0 | 0.7 | 0 | 7.2 | 0 |

FEC & CEF = cyclophosphamide + epirubicin + fluorouracil
CMF = cyclophosphamide + methotrexate + flurouracil NA = not available
Grade 1 or 2 changes in transaminase levels were observed but were more frequently seen with CMF than with CEF.

*Delayed Events*

Table 2 describes the incidence of delayed adverse events in patients participating in the MA.5 and GFEA-05 (FASG-05) trials.

**Table 2. Long-term Adverse Events in Patients with Early Breast Cancer (5-year follow-up data)***

| % of Patients | | | |
|---|---|---|---|
| **Event** | **FEC-100/CEF-120 (N=620)** | **FEC-50 (N=280)** | **CMF (N=360)** |
| **Cardiac events** | | | |
| Asymptomatic drops in LVEF | 1.8 | 1.4 | 0.8 |
| CHF | 1.5 | 0.4 | 0.3 |
| **AML/MDS** | | | |
| AML | 0.8 | 0 | 0.3 |
| MDS | 0 | 0 | 0 |

*In study MA.5 cardiac function was not monitored after 5 years. In study GFEA-05 (FASG-05) monitoring of cardiac function was optional.

Within the first 5 year follow-up period, two cases of acute lymphoid leukemia (ALL) were also observed in patients receiving epirubicin. However, an association between anthracyclines such as epirubicin and ALL has not been clearly established.

Over the 10 year follow-up period for study GFEA-05 (FASG-05), the overall incidence of cardiac events in patients treated with FEC-100 remained similar to that reported in patients receiving FEC-50. There were, however, two new cases of decreased left ventricular ejection fraction reported in FEC-100 treated patients. Therefore, the incidence of decreased left ventricular ejection fraction was 1.1% (3/280) in the FEC-50 group and 3% (8/266) in the FEC-100 group. No new cases of delayed CHF were reported. Thus the frequency of CHF remains at 0.4% (1/280) in the FEC-50 and at 1.1% (3/266) in the FEC-100 group. In a subset of patient from this study who were without disease at median follow up time of 102 months, a subsequent analysis of long term cardiac function identified 2 patients with CHF amongst the 85 FEC-100 patients evaluated (see reference 72). Cardiac function was not monitored after 5 years in MA.5 study.

No new cases of secondary leukemia were reported in the 10 year follow up for both MA.5 and GFEA-05 (FASG-05) trials.

## Postmarketing Surveillance:

Gastrointestinal: pain or burning sensation, erythema, erosions, ulcerations, bleeding, dehydration, hyperpigmentation of the oral mucosa

Cutaneous: flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)

Hypersensitivity Reactions: urticaria, anaphylaxis, fever, chills, shock

Vascular: phlebitis, thrombophlebitis

Urological: red colouration of urine for 1 to 2 days after administration

## DRUG INTERACTIONS

Epirubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see WARNINGS AND PRECAUTIONS). The use of epirubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Cimetidine increased the AUC of epirubicin by 50% when given for seven days, starting five days before chemotherapy. Cimetidine should be stopped prior to treatment with epirubicin.

## DOSAGE AND ADMINISTRATION

**Refer to SPECIAL HANDLING INSTRUCTIONS.**

### DOSAGE:

A variety of dose schedules have been used. The following recommendations are for use as a single agent or in combination with other chemotherapeutic agents.

Dosage is usually calculated on the basis of body surface area. The lower dose should be given to patients with inadequate marrow reserves due to prior therapy or neoplastic marrow infiltration. Standard starting doses and regimens have been used in the elderly.

**Hepatic Dysfunction.** As Epirubicin Hydrochloride for Injection is extensively metabolized by the liver and excreted primarily by the biliary system, its dosage must be reduced in patients with impaired liver function indicated by elevated bilirubin or serum AST values as follows: Serum bilirubin 21-51 µmol/L or AST 2 to 4 times upper limit of normal - give ½ of recommended starting dose; Serum bilirubin > 51 µmol/L or AST > 4 times upper limit of normal - give ¼ of recommended starting dose. Patients with severe hepatic impairment should not receive epirubicin (see CONTRAINDICATIONS).

**Renal Dysfunction.** While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, lower starting doses are necessary in patients with severe renal impairment (serum creatinine >5 mg/dl).

**Other Special Populations.** Lower starting doses or longer intervals between cycles may need to be considered for heavily pretreated patients or patients with neoplastic bone marrow infiltration (see WARNINGS AND PRECAUTIONS). Standard starting doses and regimens have been used in the elderly.

**CARCINOMA OF THE BREAST**

***Early Breast Cancer-Adjuvant Treatment***

Breast cancer has been managed using epirubicin in combination with various chemotherapeutic agents. The recommended adjuvant treatment of early breast cancer should employ a cyclophosphamide, epirubicin, and 5-fluorouracil combination regimen (CEF 120) in a cycle to be repeated every 4 weeks for 6 cycles as follows:

- cyclophosphamide 75 mg/m$^2$ p.o. on days 1 to14,
- epirubicin 60 mg/m$^2$ i.v. on days 1 and 8, and
- 5-fluorouracil 500 mg/m$^2$ i.v. days 1 and 8.

***Metastatic Breast Cancer***

**Single Agent:** The most commonly used dosage schedule of Epirubicin Hydrochloride for Injection in metastatic breast cancer, when employed as a single agent for adults, is 75-90 mg/m$^2$ administered at 21-day intervals. The recommended single dose may be divided over 2 successive days. An alternative weekly dosage schedule of 12.5 to 25 mg/m$^2$ has been used and has been reported to produce less clinical toxicity than higher doses given every three weeks.

**Combination Therapy:** In metastatic breast cancer, epirubicin can be used in combination with cyclophosphamide and 5-fluorouracil (FEC), at a dose of 50 mg/m$^2$.

**SMALL CELL LUNG CANCER**

**Single Agent:** Epirubicin Hydrochloride for Injection, as a single agent, can be used at 90-120 mg/m$^2$ administered every 3 weeks.

**Combination Therapy:** Epirubicin has been used in several different combinations with other antineoplastic agents at doses ranging from 50-90 mg/m$^2$. The following combinations have proven effective: Epirubicin in combination with either cisplatin or ifosfamide; epirubicin with cyclophosphamide and vincristine (CEV); epirubicin with cyclophosphamide and etoposide (CEVP-16) and epirubicin with cisplatin and etoposide.

**NON-SMALL CELL LUNG CANCER**

**Single Agent:** Epirubicin Hydrochloride for Injection, as a single agent, can be used at doses of 120-150 mg/m$^2$ administered day 1, every 3-4 weeks.

**Combination Therapy:** Epirubicin, in combination with etoposide, cisplatinum, mitomycin, vindesine and vinblastine, can be used at doses of 90-120 mg/m$^2$ administered day 1, every 3-4 weeks.

**NON-HODGKIN'S LYMPHOMA**

**Single Agent:** Epirubicin Hydrochloride for Injection, as a single agent, can be used at doses of 75-90 mg/m$^2$ at 21-day intervals.

**Combination Therapy:** Epirubicin at doses of 60-75 mg/m$^2$ can be used in combination with cyclophosphamide, vincristine and prednisone with or without bleomycin (replacing doxorubicin in the CHOP, CHOP-Bleo or BACOP regimens) for the treatment of newly diagnosed non-Hodgkin's lymphoma.

**HODGKIN'S DISEASE**
**Combination Therapy:** Epirubicin, in combination with bleomycin, vinblastine and dacarbazine, can be used at 35 mg/m$^2$ every 2 weeks or 70 mg/m$^2$ every 3-4 weeks (replacing doxorubicin in the ABVD regimen).

**OVARIAN CANCER**
**Single Agent:** In patients with prior therapy, epirubicin can be used as single agent at doses of 50-90 mg/m$^2$ at 3-4 week intervals.

**Combination Therapy:** In patients with prior therapy epirubicin can be used in combination at doses of 50-90 mg/m$^2$ at 3-4 week intervals. Epirubicin at doses of 50-90 mg/m$^2$ in combination with cisplatin and cyclophosphamide can be used for initial therapy of ovarian cancer repeated at 3-4 week intervals.

**GASTRIC CANCER**
**Single Agent:** Epirubicin, as a single agent, can be used for the treatment of locally unresectable or metastatic gastric carcinoma at doses of 75-100 mg/m$^2$.

**Combination Therapy:** Epirubicin, at a dose of 80 mg/m$^2$ can be used in combination with fluorouracil for the treatment of locally unresectable or metastatic gastric carcinoma.

## ADMINISTRATION:

Care in the administration of Epirubicin Hydrochloride for Injection will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of Epirubicin Hydrochloride for Injection, extravasation may occur with or without an accompanying stinging or burning sensation even if the blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that subcutaneous extravasation has occurred, the following steps are recommended:

1. Attempt aspiration of the infiltrated Epirubicin Hydrochloride for Injection solution.

2. Local intermittent application of ice for up to 3 days.

3. Elevation of the affected limb.

4. Close observation of the lesion.

5. Consultation with a plastic surgeon familiar with drug extravasation if local pain persists or skin changes progress after 3 to 4 days. If ulceration begins, early wide excision of the involved area should be considered.

Epirubicin Hydrochloride for Injection 50 mg vial should be reconstituted with 25 mL of Water for Injection (WFI) to give a final concentration of 2 mg/mL of epirubicin hydrochloride.

Alternatively, Epirubicin Hydrochloride for Injection 50 mg vials can also be reconstituted with 25 mL of Sodium Chloride Solution U.S.P. (0.9%) to give a final concentration of 2 mg/mL of epirubicin hydrochloride. However, it should be noted that **reconstitution in saline will result in a longer reconstitution time**.

Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken until the contents are dissolved. A slight suspension may form which will completely dissolve on further shaking. The vials are under negative pressure and care should be taken to avoid a pressure build up. The reconstituted solution using WFI is stable for 24 hours at room temperature and 48 hours under refrigeration at 2-8°C. Alternatively, if 0.9% Sodium Chloride was used as the reconstituting diluent, the solution has been shown to be stable for 48 hours at room temperature and 2-8°C. The solution should be protected from exposure to direct light and any unused solution should be discarded.

Epirubicin Hydrochloride for Injection should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Solution USP (0.9%) or 5% Dextrose Solution USP. The tubing should be attached to a Butterfly® needle or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. To minimize the risk of thrombosis or perivenous extravasation, the usual infusion times range between 3 and 20 minutes depending upon dosage and volume of the infusion solution. The infusion time should be not less than 3 to 5 minutes. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see WARNINGS AND PRECAUTIONS). Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Unless specific compatibility data are available, mixing Epirubicin Hydrochloride for Injection with other drugs is not recommended.

Epirubicin Hydrochloride for Injection has been used concurrently with other approved chemotherapeutic agents. Evidence is available that combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated.

**For Safe Preparation and Handling of Epirubicin Hydrochloride for Injection refer to "SPECIAL HANDLING INSTRUCTIONS".**

## OVERDOSAGE

Acute overdosage with Epirubicin Hydrochloride for Injection may cause an acute myocardial dysfunction within 24 hours. Pronounced mucositis, leukopenia and thrombocytopenia could be observed within 7-14 days. Treatment of acute overdosage consists of hospitalization of the severely myelosuppressed patient, platelet and granulocyte transfusions, antibiotics, and symptomatic treatment of mucositis.

## ACTION AND CLINICAL PHARMACOLOGY

The mechanism of action of epirubicin, although not completely elucidated, appears to be related to its ability to bind to nucleic acids by intercalation of the planar anthracycline nucleus with the DNA double helix.

Binding to cell membranes as well as to plasma proteins may also be involved. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity, mutagenesis and chromosomal aberrations.

Animal studies have shown activity in a wide spectrum of experimental tumours, immunosuppression, mutagenic and carcinogenic properties in rodents, and a variety of toxic effects, including myelosuppression in all species and atrophy of the seminiferous tubules of testes in rats and dogs.

Data from different animal species and ***in vitro*** models have shown that epirubicin is less toxic, and in particular less cardiotoxic than doxorubicin.

At equally effective doses, epirubicin produces less severe non-hematologic side effects such as vomiting and mucositis, than doxorubicin.

**Early Stage Breast Cancer Studies:**

Two randomized, open-label, multi center studies evaluated Epirubicin Hydrochloride for Injection 100 to 120 mg/m$^2$ in combination with cyclophosphamide and fluorouracil in adjuvant treatment of axillarynode-positive breast cancer with no evidence of distant metastatic disease. (See CLINICAL TRIALS for complete study descriptions and overall results; see ADVERSE REACTIONS.)

Study MA.5 evaluated 120 mg/m$^2$ doses of epirubicin per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen) versus a CMF (methotrexate) regimen in pre- and peri-menopausal women.

Study GFEA-05 (FASG-05) evaluated 100 mg/m$^2$ doses of epirubicin per course in combination with fluorouracil and cyclophosphamide (FEC-100) or lower-dose FEC-50 in pre- and postmenopausal women.

In the pivotal trial MA.5, the Cox proportional model showed that node number is a significant ($p=0.0001$) outcome predictor overall (conditional risk ratio of 1.7 for $\geq 4$ versus $< 3$ involved nodes). Non-significant trends indicate that the CEF treatment may show superiority over CMF in patients with $\geq 4$ nodes than those with $< 3$. The trial was insufficiently powered to demonstrate a subset difference; it must be borne in mind that the majority of patients (61%) in both treatments had 1-3 positive nodes, yet CEF-120 still produced overall advantages in relapse free survival (RFS) and overall survival (OS) (see below and CLINICAL TRIALS). Nonetheless, CEF versus CMF RFS in the $< 3$ node group was 68 vs. 62%, while in the $\geq 4$ node group the values were 52 vs. 39%.

In the supporting trial GFEA-05 (FASG-05), similar improvements in RFS and OS were observed in both pre- and postmenopausal women treated with FEC-100 compared to FEC-50.

Overall efficacy results for the two studies are shown in Table 4 (see CLINICAL TRIALS). The median follow-up time in the MA.5 study was 8.8 years (range: 0.2 to 12.1 years) and 8.7 years (range: 0.7 to 12.1 years) for the CEF and CMF treatment groups, respectively. In MA.5, the CEF-120 therapy demonstrated superior RFS to CMF, both over the 5- and 10-year followup. The overall reduction in risk of relapse was 24% over 5 years and 22% over 10 years. The 5- and 10-year OS were also greater for the epirubicin-containing CEF-120 regimen than for the CMF regimen. The overall relative reduction in the risk of death was 29% over 5 years and 18% over 10 years.

**Pharmacokinetics:**

Pharmacokinetic studies show an initial rapid elimination of the parent compound from plasma. The terminal half-life of elimination of the parent drug from plasma approximates 30-40 hours in humans. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours. Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel to those of the unchanged drug.

Impairment of hepatic function results in higher plasma levels.

Distribution studies in the rat have shown that epirubicin does not appear to cross the blood-brain barrier.

## STORAGE AND STABILITY

Epirubicin Hydrochloride for Injection should be stored at 15-30°C and protected from light.

RECONSTITUTED SOLUTIONS

Recommended Diluents for Reconstitution:
Water for Injection (WFI)
0.9% Sodium chloride Injection USP
(without bacteriostatic agent)

## RECONSTITUTION TABLE

| Vial Size | Diluent Added To Vial (mL) | Approximate Available Volume (mL) | Approximate Concentration (mg/mL) |
|---|---|---|---|
| 50 mg | 25 | 25 | 2 |

See Preparation of Solution for instructions.

The solution should be protected from exposure to direct light and any unused solution should be discarded. Please refer to the table below for a summary of the stability of the solutions once it has been reconstituted.

| Reconstituting Diluent | At Room Temperature | At 2-8°C |
|---|---|---|
| WFI | 24 hours | 48 hours |
| 0.9% Sodium Chloride | 24 hours | 48 hours |

Incompatibility:
Unless specific compatibility data are available, Epirubicin Hydrochloride for Injection should not be mixed with other drugs.

Contact with any solution of an alkaline pH should be avoided, as it will result in hydrolysis of the drug. Epirubicin should also not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

## SPECIAL HANDLING INSTRUCTIONS

**Preparation and Handling:**

1. Personnel should be trained in good technique for reconstitution and handling. Pregnant staff should be excluded from working with this drug.

2. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II) and the work surface should be protected by disposable, plastic-backed absorbent paper.

3. Personnel handling epirubicin solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks. If epirubicin solutions contact the skin or mucosa, the area should be washed with soap and water or sodium bicarbonate immediately. Do not abrade the skin by using a scrub brush and always wash hands after removing gloves.

4. In case of contact with the eye(s), hold back the eyelid of the affected eye(s) and flush with copious amounts of water for at least 15 minutes, proceed to a physician for medical evaluation.

5. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

**Disposal;**

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials and other materials which have come in contact with epirubicin should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, epirubicin hydrochloride may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolourize the epirubicin, care being taken to vent the vial to avoid a pressure build-up of the chlorine gas which is generated. Dispose of detoxified vials in a safe manner.

**Needles, syringes, disposable and non-disposable equipment:**

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution in the sewer system with running water and discard disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

**Spillage/Contamination:**

Wear gloves, mask, protective clothing. Treat spilled liquid with sodium hypochlorite solution. Carefully absorb solution with gauze pads or towels, wash area with water and absorb with gauze or towels again and place in a polyethylene bag; seal, double bag and mark as hazardous waste. Disposal of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean up should wash with soap and water.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Epirubicin Hydrochloride for Injection is available in 50 mg vials for intravenous use.

The 50 mg vials are packaged and supplied in single vial cartons.

**Composition:**

Epirubicin Hydrochloride for Injection is supplied as a sterile red-orange lyophilized powder.

50 mg glass vials - Each vial contains 50.3 mg of epirubicin hydrochloride and 251.5 mg of lactose monohydrate. To withdraw exact amount.

The 50 mg glass vials are packaged in single vial cartons.

## PART II: SCIENTIFIC INFORMATION

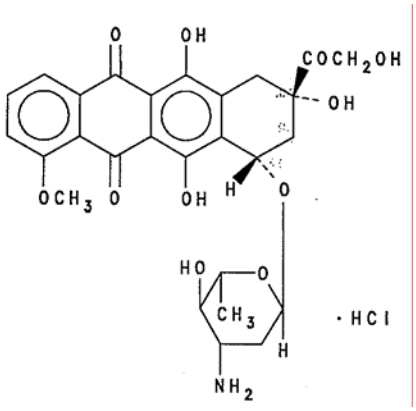
## PHARMACEUTICAL INFORMATION

**Drug Substance**

**Proper Name:** Epirubicin Hydrochloride

**Chemical Name:** 5,12-Naphthacenedione,10-[(3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1- methoxy-, hydrochloride, (8S-cis)-

**Structural Formula:**




**Molecular Formula:** $C_{27}H_{29}NO_{11}$. HCl

**Molecular Weight:** 579.99

**Description:**

Epirubicin hydrochloride is a semisynthetic anthracycline cytotoxic antibiotic in which the sugar moiety differs from the natural daunosamine (amino sugar present in doxorubicin) in that steric configuration of the hydroxyl bearing C-4 is inverted, thus forming the L-arabino configuration instead of the L-lyxo. The anthracycline ring is lipophilic. The saturated end of the ring system contains hydroxyl groups adjacent to the amino sugar producing a hydrophilic centre. The molecule is amphoteric, containing acidic function in the phenolic ring groups and a basic function in the sugar amino group.

It is a dark red crystalline powder, soluble in water, methanol and ethyl alcohol (50°C). It is practically insoluble in acetone, chloroform and methylene chloride. Epirubicin hydrochloride has a melting point of 173-177°C, pKa in water of 7.7, and pH of 4-5.5 in a 0.5% w/v solution in water.

## CLINICAL TRIALS

Early Stage Breast Cancer Studies (see ADVERSE REACTIONS)

Two randomized, open-label, multi center studies evaluated the use of epirubicin hydrochloride injection 100 to 120 mg/m$^2$ in combination with cyclophosphamide and fluorouracil for the adjuvant treatment in 1281 women with:

- axillary-node-positive breast cancer,
- no evidence of distant metastatic disease (Stage II or III), and
- no T4 tumors.

Study MA.5 evaluated 120 mg/m$^2$ of epirubicin per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). Pre- and peri-menopausal women with one or more positive lymph nodes were randomized to either the CEF-120 regimen or a CMF regimen.

Study GFEA-05 (FASG-05) evaluated the use of 100 mg/m$^2$ of epirubicin per course in combination with fluorouracil and cyclophosphamide (FEC-100). Pre- and postmenopausal women were randomized to either the FEC-100 or lower-dose FEC-50 regimens. Eligible patients were either required to have 4 nodes involved with tumour or, if only 1 to 3 nodes were positive, to have negative estrogen- and progesterone-receptors and a histologic tumour grade of 2 or 3.

Table 3 shows the treatment regimens that the patients received.

**Table 3. Treatment Regimens Used in Early Breast Cancer Phase 3 Studies**

| | Treatment Groups | Agent | Regimen |
|---|---|---|---|
| MA.5[1]<br>N=716 | **CEF-120** (total, 6 cycles)[2]<br><br>N=356 | Cyclophosphamide | 75 mg/m$^2$ PO<br>d 1-14, q 28 days |
| | | Epirubicin | 60 mg/m$^2$IV<br>d 1 & 8, q 28 days |
| | | Fluorouracil | 500 mg/m$^2$ IV<br>d 1 & 8, q 28 days |
| | **CMF** (total, 6 cycles)<br><br>N=360 | Cyclophosphamide | 100 mg/m2 PO<br>day 1-14, q 28 days |
| | | Methotrexate | 40 mg/m$^2$ IV<br>day 1 & 8, q 28 days |
| | | Fluorouracil | 600 mg/m$^2$ IV<br>d 1 & 8, q 28 days |
| GFEA-05<br>(FASG-05)[3]<br><br>N=565 | **FEC-100** (total, 6 cycles)<br><br>N=276 | Fluorouracil | 500 mg/m$^2$ IV<br>day 1, q 21 days |
| | | Epirubicin | 100 mg/m$^2$IV<br>day 1, q 21 days |
| | | Cyclophosphamide | 500 mg/m$^2$IV<br>day 1, q 21 days |
| | **FEC-50** (total, 6 cycles)<br><br>N=289 | Fluorouracil | 500 mg/m$^2$IV<br>day 1, q 21 days |
| | | Epirubicin | 50 mg/m$^2$IV<br>day 1, q 21 days |
| | Tamoxifen 30 mg daily x 3 years, postmenopausal women, any receptor status. | Cyclophosphamide | 500 mg/m$^2$ IV<br>day 1, 21 days |

[1] In women who underwent lumpectomy, breast irradiation was to be administered after completion of study chemotherapy.

[2] Patients also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or fluroquinolone for the duration of their chemotherapy.

[3] All women were to receive breast irradiation after the completion of chemotherapy.

The efficacy endpoints of relapse-free survival (RFS) and overall survival (OS) were analyzed using Kaplan-Meier methods in the intent-to-treat (ITT) patient populations in each study. Results for endpoints are described in terms of the outcomes over 5 and 10 years

.

MA.5 results: The median age of the study population was 45 years. Approximately 60% of patients had 1 to 3 involved nodes and approximately 40% had ≥ 4 nodes involved with tumor. The median follow-up time was 8.8 years (range: 0.2 to 12.1 years) and 8.7 years (range: 0.7 to 12.1 years) for the CEF and CMF treatment groups, respectively. The epirubicin-containing combination therapy (CEF-120) demonstrated superior RFS to CMF, both over the 5- and 10-year follow-up (Table 4). The overall reduction in risk of relapse was 24% over 5 years and 22% over 10 years. The 5- and 10-year OS were also greater for the CEF-120 regimen than for the CMF regimen (Table 4). The overall relative reduction in the risk of death was 29% over 5 years and 18% over 10 years.

GFEA-05 (FASG-05) results: The median age was 51 years and approximately half of the patients were postmenopausal. About 17% of the study population had 1 to 3 positive nodes and 80% of patients had ≥ 4 involved lymph nodes. Demographic and tumor characteristics were well-balanced between treatment arms in each study. The median follow-up time was 7.7 years (range: 0.3 to 12.5 years) and 8.7 years (range: 0.2 to 12.7 years) in the FEC-50 and FEC-100 treatment groups, respectively. Patients treated with the higher-dose epirubicin regimen (FEC-100) had a significantly longer RFS and OS over 5- and 10-years (Table 4) than patients given the lower dose regimen (FEC-50). The overall reduction in risk of relapse was 32% over 5 years and 22% over 10 years. The relative reduction in the risk of death was 31% over 5 years and 25% over 10 years.

Although the trials were not powered for subgroup analyses, in the MA-5 study improvement in favor of CEF-120 vs. CMF were observed over 5- and 10-years in RFS and OS both in patients with 1-3 node positive and those with ≥ 4 node positive tumor involvement. In the GFEA-05 (FASG-05) study, improvements in RFS and OS were observed over 5- and 10-years in both pre- and postmenopausal women treated with FEC-100 compared to FEC-50.

Efficacy results for the two studies are shown in Table 4.

**Table 4. Efficacy Results from Early Breast Cancer Phase 3 Studies***

| | MA.5 Study | | GFEA-05 (FASG-05) Study | |
|---|---|---|---|---|
| | CEF-120<br>N = 356 | CMF<br>N = 360 | FEC-100<br>N = 276 | FEC-50<br>N = 289 |
| RFS over 5 yrs (%) | 62 | 53 | 65 | 52 |
| Log-Rank Test | (stratified p = 0.013 | | (p = 0.007) | |
| OS over 5 yrs (%) | 77 | 70 | 76 | 65 |
| Log-Rank Test | (stratified p = 0.043)<br>(unstratified p = 0.13) | | (p = 0.007) | |
| RFS over 10 yrs (%) | 51 | 44 | 49 | 43 |
| Log-Rank Test (stratified) | (p = 0.017) | | (p = 0.040) | |
| OS over 10 yrs (%) | 61 | 57 | 56 | 50 |
| Log-Rank Test (stratified) | (p = 0.100) | | (p = 0.023) | |
| *Based on Kaplain-Meier estimates | | | | |

The Kaplain-Meier curves for RFS and OS from Study MA.5 are shown in Figures 1 and 2 and those for Study GFEA-05 (FASG-05) are shown in Figure 3 and 4.

**Figure 1. Relapse-Free Survival in Study MA-5**

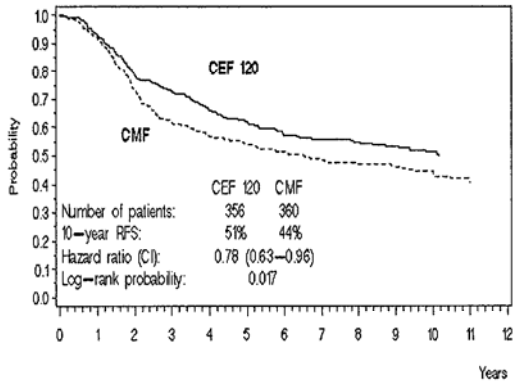



**Figure 2. Overall Survival in Study MA-5**

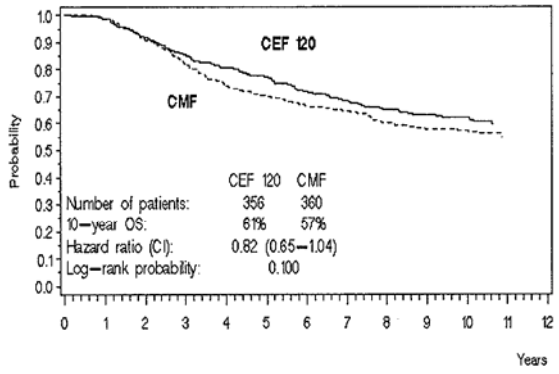



**Figure 3. Relapse-Free Survival in Study GFEA-05 (FASG-05)**

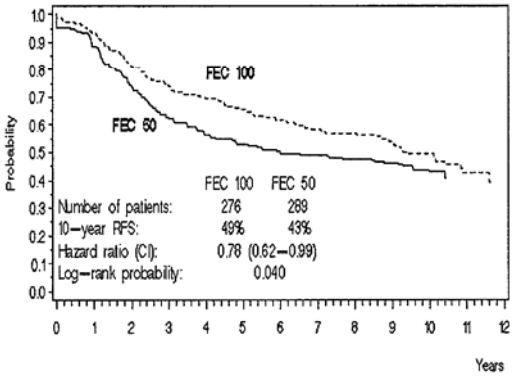
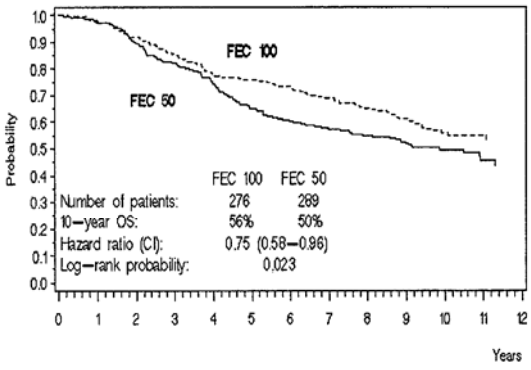



**Figure 4. Overall Survival in Study GFEA-05 (FASG-05)**



## DETAILED PHARMACOLOGY

The *in vitro* cytotoxicity of epirubicin, compared to doxorubicin, was investigated using the HeLa cloning efficiency test, the human tumour stem cell assay and the inhibition of mouse embryo fibroblast proliferation test. In the first test, epirubicin had less activity than doxorubicin. In the other two tests the activity of the two compounds was similar.

The antitumoural activity of epirubicin was compared with doxorubicin on various mouse experimental tumours. Administered i.p. or i.v as a single injection (sarcoma 180 ascites, leukemia L1210, leukemia P388, Gross leukemia), the two compounds had the same antitumour effect at the same dose. One sub-line of leukemia P388 resistant to doxorubicin showed cross-resistance to epirubicin. Administered i.v and at the same dose, the two compounds had exactly the same effect on solid sarcoma 180 and on both advanced and early mammary carcinoma.

The antitumoural effect of epirubicin was slightly greater than that of doxorubicin on Lewis lung carcinoma and MS-2 sarcoma lung metastases and also on MSV-induced rhabdomyosarcoma and on colon 38 adenocarcinoma.

Epirubicin was found active on mammary carcinoma, melanoma, epidermoid carcinoma of the lung and soft tissue sarcoma, transplanted to nude mice.

Epirubicin was found active against breast, lung, prostate and ovarian tumours transplanted in nude mice; it showed particularly good activity against melanomas. No statistically significant effect was observed against colorectal human tumours transplanted into nude mice.

Pharmacokinetic studies in man show an initial rapid elimination of the parent compound from plasma. The terminal half-life of elimination of the parent drug from plasma approximates 30-40 hours. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours. Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubincol.

Glucuronidation distinguishes epirubicin from doxorubicin and may account for its reduced toxicity. Other metabolites found are aglycones of 7-deoxydoxorubicin and 7deoxydoxorubinicol. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel to those of the unchanged drug.

## TOXICOLOGY

The acute toxicity of epirubicin i.v was studied in the mouse, rat and dog.

In the mouse, single doses caused dose-dependent deaths between the $4^{th}$ and $180^{th}$ day after injection. Calculated at stabilization, the $LD_{50}$ was 15.06 mg/kg.

In the rat, single doses of epirubicin produced dose-dependent mortality between the $4^{th}$ and $15^{th}$ day after injection. Calculated at stabilization, the $LD_{50}$ was 13.95 mg/kg.

In the dog, single doses were lethal at 2 mg/kg, while the lower dose (1 mg/kg) can be held to be just within the safety limit.

Chronic toxicity studies were carried out in the rabbit and in the dog after i.v courses of three consecutive days per week for a total of 6 weeks on the rabbit and 6 and 13 weeks in the dog. The results showed that, in the rabbit, the pharmacological-toxicological mechanism of action of epirubicin is very similar to that of doxorubicin. In qualitative terms, epirubicin is very similar to that of doxorubicin. In quantitative terms, epirubicin was approximately one-third less toxic than doxorubicin with respect to systemic toxicity and myocardial toxicity.

In the dog, the two drugs had the same toxicity profile. The safe dose of epirubicin can be set at 0.1 mg/kg in this species.

*In vitro* cardiotoxicity tests showed that epirubicin was less cardiotoxic than doxorubicin (on isolated rabbit heart and guinea pig heart); unlike doxorubicin, sometimes it had no effect at all on myocardial cells from newborn mice.

*In vivo* cardiotoxicity tests showed that in all the animal species tested (mouse i.v, rat i.p., rabbit i.v) epirubicin was appreciably less cardiotoxic than doxorubicin.

Ultrastructural studies of myocardial tissue from hamsters treated i.p. with epirubicin and doxorubicin showed that the two drugs produce similar alterations in the same length of time. Carcinogenesis tests *in vivo* run in newborn rats treated with epirubicin s.c. showed that the drug had considerable carcinogenic activity. Mutagenic activity of epirubicin was investigated in various *in vitro* and *in vivo* tests. In the *in vitro* and *in vivo* tests, *Schizosccharomyces pombe* P1, epirubicin showed no mutagenic activity; it was mutagenic, however, *in vitro* on *Salmonella typhimurium.*

Epirubicin has not shown teratogenic effects in rats or rabbits; embryotoxicity and/or abortions were seen in both species only at very high doses.

## REFERENCES


1. Ganzina F. 4'epi-doxorubicin, a new analogue of doxorubicin: A preliminary overview of preclinical and clinical data. Cancer Treat Rev 1983; 10:1-22.

2. Jones WG, Mattsson W. Phase II study of weekly low-dose 4'-epi-doxorubicin in advance postmenopausal breast cancer. Cancer Treat Rep 1984; 68:675-677.

3. Bonfante V, Villani F, Bonadonna G. Toxic and therapeutic activity of 4'-epidoxorubicin. Tumori 1982; 68:105-111.

4. Hurteloup P, Cappelaere P, Armand JP, Mathe G. Phase II clinical evaluation of 4'-epidoxorubicin. Cancer Treat Rep 1983; 67:337-341.

5. Rozencweig M et al. Randomized phase II trial of carminomycin versus 4'-epidoxorubicin in advanced breast cancer. J. of Clinical Oncology 1984; 2:4:275-281.

6. Robustelli della Cuna G et al. Clinical evaluation of 4'-epi-doxorubicin in advanced solid tumours. Investigational New Drugs 1983; 1:349-353.

7. Coombes RC, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. The international collaborative cancer group. J Clin Oncol 1996; 14(1):35-45.

8. Brufman G, et al. Doubling epirubicin dose intensity (100 mg/m$^2$ versus 50 mg/m$^2$) in the FEC regimen significantly increases response rates. An international randomised phase III study in metastatic breast cancer. Ann Oncol 1997; 8:155-162.

9. Pyrhonen SO, Kouri MO. Phase II study of epirubicin sequential methotrexate and 5-fluorouracil for advanced colorectal cancer. Eur J. Cancer 1992; 28A (11):1828-1832.

10. Raderer et al. Tolerance of the novel chemo-sensitizer dexverapamil in combination with anthracycline chemotherapy: a prospective toxicity analysis in advanced gastrointestinal cancer. Onkologie 1995; 18(5):462-467.

11. Michaelson R, Kemeny N, Young C. Phase II evaluation of 4'-epi-doxorubicin in patients with advanced colorectal carcinoma. Cancer Treat Rep 1982; 66(9):1757-1758.

12. Martoni A, Tomasi L, Farabegoli G, Giovannini M, Monetti N, Ganzina F, Pannuti F. The phase II study of 4'-epi-doxorubicin plus cisplatinum in advanced solid tumours. Eur J Cancer Clin Oncol 1984; 20:1:11-17.

13. Wils J, et al. Cyclophosphamide, epirubicin and cisplatin (CEP versus epirubicin plus cisplatin (EP) in stage Ic-IV ovarian cancer: a randomized phase III trial of the gynecologic oncology group of the comprehensive cancer center Limburg. Anti-Cancer Drugs 1999; 10:257-261.

14. Conte PF, et al. High-dose versus low-dose cisplatin in combination with cyclophosphamide and epidoxorubicin in suboptimal ovarian cancer: a randomized study of the gruppo oncologico Nord-Ovest. J Clin Oncol 1996; 14(2):351-356.

15. Peláez, et al. Phase II trial of epirubicin at standard dose in relapsed ovarian cancer. Eur J Cancer 1996; 32A(5):899-900.

16. Pronzato P, et al. A feasibility study of accelerated polychemotherapy with cisplatin, epidoxorubicin and cyclophosphamide (PEC) in advanced ovarian cancer. Br J Ca 1996; 73:1425-1427.

17. Villani F, Comazzi R, Lacaita G, Genitoni V, Guindani A, Martini A. Preliminary echocardiographic and polygraphic evaluation of cardiac toxicity of 4'-epi-doxorubicin. International Journal of Clinical Pharmacology, Therapy and Toxicology 1983; 21:4:203-208.

18. Weenen H, Van Maanen JMS, De Planque MM, McVie JG, Pinedo HM. Metabolism of 4'-modified analogs of doxorubicin. Unique glucuronidation pathway for 4'epidoxorubicin. Eur J Cancer Clin Oncol 1984; 20:7:919-926.

19. Topham C. et al: Randomised trial of epirubicin alone versus 5-fluorouracil, epirubicin and mitomycin C in locally advanced and metastatic carcinoma of the pancreas. Br J Cancer 1991; 64;179-181.

20. Wagener DJ.TH, et al. Results of a phase II trial of epirubicin and cisplatin (EP) before and after irradiation and 5-fluorouracil in locally advanced pancreatic cancer: an EORTC GITCCG study. Eur J Cancer 1996; 32A(8):1310-1313.

21. Martoni A, Giovannini M, Tomasi L, Camaggi CM, Bellanova B, Monetti N, Rossini G, Tarquinni M, Martini A, Panutti F. A phase II clinical trial of 4'-epi-doxorubicin in advanced solid tunours. Cancer Chemother Pharmacol 1984; 12:179-182.

22. Bonadonna G. Advances in anthracycline chemotherapy: Epirubicin. Masson Italia Editori, Milan 1984.

23. Wils J et al. Phase II study of epirubicin in advanced adenocarcinoma of the pancreas. Eur J Cancer Clin Oncol 1985; 21:2:191-194.

24. Bezwoda WR, Treatment of advanced ovarian cancer: A randomized trial comparing Adriamycin or 4'-epi-Adriamycin in combination with cisplatin and cyclophosphamide. Med and Ped Oncology 1986; 14:26-29.

25. Walder S, Green M, Muggia F. The role of anthracyclines in the treatment of gastric cancer. Cancer Treat Rev 1985; 12:105-132.

26. Brambilla C, Rossi A, Bonfante V, Ferrari L, Villani F, Crippa F, Bonadonna G. Phase II study of doxorubicin versus epirubicin in advance breast cancer. Cancer Treat Rep 1986; 70:2:261-266.

27. Hochester H, Green MD, Speyer JL, Wernz JC, Blum RH, Muggia FM. Activity of epirubicin in pancreatic carcinoma. Cancer Treat Rep 1986; 70:2:299-300.

28. Lopez M et al. Epirubicin in non-Hodgkin's lymphoma. Am J Clin Oncol 1985; 8:151-153.

29. Eridani S, Pearson TC, Slater NGP, Singh AK. A pilot study of epirubicin (NSC 256942) in combination treatment of acute leukemia and non-Hodgkin's lymphoma. Oncology 1984; 41:383-386.

30. Avilés A, et al. Results of a randomized study of early stage Hodgkin's disease using ABVD, EBVD, or MBVD. Med Pediatr Oncol 1995; 24:171-175.

31. Gobbi PG, et al. MOOP/EBV/CAD hybrid chemotherapy with or without limited radiotherapy in advanced or unfavorably presenting Hodgkin's disease: a report from the Italian lymphoma study group. J Clin Oncol 1993; 11(4):712-719.

32. Martoni A, Tomasi L, Farabegoli G, Fruet F, Panutti F. 4'-epi-doxorubicin in combination with cisplatin in advanced ovarian cancer. Cancer Treat Rep 1984; 68:11.

33. Christmann D. Epirubicin in der kombinations-chemotherapie des metastasierten mammakarzinoms (VEC) und des fortgeschrittenen ovarialkarzinoms (PEC). Onkologie 1986; 9:1:11-12.

34. Scarffe JH, Kenny JB, Johnson RJ, Owens SE, Giles GR, Leveson SH, Maley WV. Phase II trial of epirubicin in gastric cancer. Cancer Treat Rep 1985; 69:11:1275-1277.

35. Kolaric K, Potrebica V, Cervek J. Phase II clinical trials of 4'-epi-doxorubicin in metastatic solid tumors. J of Cancer Research and Clin Oncol 1983; 106:2:148-152.

36. Ferrazzi E, Nocoletto O, Vinante O, Pagnin P, Maraglino G, Ganzina F, Florentino V. Phase II study of 4'-epi-doxorubicin. Tumori 1982; 68:431-435.

37. Kolaric K, Potrebica V, Stanovnik M. Controlled phase III clinical study of 4'-epidoxorubicin + 5-fluorouracil vs 5-fluorouracil alone in metastatic gastric and rectosigmoid cancer. 3rd European Conference on Clinical Oncology and Cancer Nursing. June 16-20, 1985, Stockholm, Sweden 1985; 105.

38. Blackstein M, Eisenhauer E, Wierzbicki R. Phase II study of epiribucin in extensive small cell lung cancer. Unpublished. Final report prepared by E. Eisenhauer of the National Cancer Institute of Canada. Data on file.

39. Fetscher S, et al. Dose-intense therapy with etoposide, ifosfamide, cisplatin, and epirubicin (VIP-E) in 100 consecutive patients with limited- and extensive-disease small cell lung cancer. Ann Oncol 1997; 8:49-56.

40. Jassem J, et al. Combination chemotherapy with vincristine, epirubicin and cyclophosphamide in small cell lung carcinoma. Eur J Cancer 1992; 28(2/3):473-476.

41. Blackstein M. Epirubicin in extensive small-cell lung cancer: a phase II study in previously untreated patients: a national cancer institute of Canada clinical trials group study. J Clin Oncol 1990; 8(3):385-389.

42. A randomized, double-blind clinical study comparing cyclophosphamide, epirubicin, and vincristine to cyclophosphamide, doxorubicin, and vincristine in the treatment of small cell bronchogenic carcinoma. Data on file.

43. Feld R, Wierzbicki R, Walde D, Shepherd F, Evans WK, Gupta S, Shannon P, Lassus M. Phase I-II study of high dose epirubicin in advanced non-small cell lung cancer. Unpublished. Data on file.

44. Henss H, Fiebig HH, Holdener EE, Kaplan E. Phase II study of high dose epirubicin in non-small cell lung cancer. Contrib Oncol 1989; 37: 126-140.

45. Martoni A. et al: A phase II study of high-dose epirubicin plus cisplatinum in advanced non-small-cell lung cancer (NSCLC). Annals of Oncology 1992; 3; 864-866.

46. Fetscher S, et al. Dose-intense therapy with etoposide, ifosfamide, cisplatin, and epirubicin (VIP-E) in 107 consecutive patients with limited- and extensive-stage nonsmall- cell lung cancer. Ann Oncol 1997; 8:57-64.

47. Comella P, et al. Alternated approach with local irradiation and combination chemotherapy including cisplatin or carboplatin plus epirubicin and etoposide in intermediate stage non-small-cell lung cancer. Cancer 1994; 74:1874-1881.

48. Feld R, et al. Phase I-II study of high-dose epirubicin in advanced non-small-cell lung cancer. J Clin Oncol 1992;10(2):297-303.

49. Smit EF, et al. A phase II study of high dose epirubicin in unresectable non small cell lung cancer. Br J Cancer 1992; 65(3):405-408.

50. Wils J, Utama I, Sala L, Smeets J, Riva A. Phase II Study of High Dose Epirubicin in Non-Small Cell Lung Cancer 1990; 26: 1140-1141.

51. Levine MN, Bramwell VH, Pritchard KI, et. al. Randomized Trial of Intensive Cyclophosphamide, Epirubicin, and Fluorouracil Chemotherapy Compared With Cyclophosphamide, Methotrexate, and Fluorouracil in Premenopausal Women With Node-Positive Breast Cancer. J Clin Oncol. 1998; 16: 2651-2658.

52. Praga C, et al. Anthracycline-induced cardiotoxicity and its relevance in cancer treatment. In Nimmo WS & AL: Clinical Measurement in Drug Evaluation. Wolfe, Publishing Ltd, London, 1991, 131-142.

53. Camaggi C.M. et al: Epirubicin plasma and blood pharmacokinetics after single i.v. bolus in advanced cancer patients. Drugs Exp Clin Res 1985; 11(4):285-294.

54. Twelves C.J. et al: Clinical pharmacokinetics of epirubicin: the importance of liver biochemistry tests. Br J Cancer 1992; 66(4):765-769.

55. Camaggi CM, et al. Pharmacokinetic studies of 4'-epidoxorubicin in cancer patients with normal and impaired renal function and with hepatic metastases. Cancer Treat Rep 1982; 66(10):1819-1824.

56. Bauer KA, Levine M. Evaluation and management of the cancer patient with thrombosis. In: American Society of Clinical Oncology (ASCO) Educational Book 1999; 223-233.

57. Mazué G, Williams GM, Iatropoulos MJ, et al. Anthracyclines: review of genotoxicity and carcinogenicity studies. Int J Oncol 1996; 8:525-536.

58. Murry LS, et al. The effect of cimetidine on the pharmacokinetics of epirubicin in patients with advanced breast cancer: preliminary evidence of a potentially common interaction. Clin Oncol (Royal College of Radiologists) 1998; 10(1):35-38.

59. El Helw LM, Lorigan PC, Robinson MH, et al. VEDex (vincristine, epirubicin dexamethasone): an effective and well-tolerated palliative chemotherapy regimen for non-Hodgkin's lymphoma. Int J Oncol 2000;16(4):777-782.

60. Bocchia M, Bigazzi C, Marconcini S, et al. Favorable impact of low-dose fludarabine plus epirubicin and cyclophosphamide regimen (FLEC) as treatment for low-grade non- Hodgkin's lymphomas. Haematologica 1999;84(8):716-720.

61. Aviles A, Nambo MJ, Talavera A, et al. Epirubicin (CEOP-Bleo) versus idarubicin (CIOP-Bleo) in the treatment of elderly patients with aggressive non-Hodgkin's lymphoma: dose escalation studies. Anti-Cancer Drugs 1997;8(10):937-942.

62. Bertini M, Freilone R, Vitolo U, et al. The treatment of elderly patients with aggressive non-Hodgkin's lymphomas: feasibility and efficacy of an intensive multidrug regimen. Leukemia & Lymphoma 1996;22(5-6):483-493.

63. Lambertenghi Deliliers G, Butti C, et al. A cooperative study of epirubicin with cyclophosphamide, vincristine and prednisone (CEOP) in non-Hodgkin's lymphoma. Haematologica 1995;80(4):318-324.

64. Huan SD, Stewart DJ, Aitken SE, et al. Combination of epirubicin and cisplatin in hormone-refractory metastatic prostate cancer. Am J Clin Oncol 1999;22(5):471-474.

65. Veronesi A, Re GL, Foladore S, et al. Multidrug chemotherapy in the treatment of nonelderly patients with hormone-refractory prostatic carcinoma. A phase II study. North- Eastern Italian Oncology Group (GOCCNE). Eur Urol 1996;29(4):434-438.

66. Veronesi A, Lo Re G, Carbone A, et al. Multimodal treatment of locally advanced transitional cell bladder carcinoma in elderly patients. Eur J Cancer 1994;30A(7):918-920.

67. Quoix EA, Giaccone G, Jassem J, et al. Epirubicin in previously untreated patients with small cell lung cancer: a phase II study by the EORTC Lung Cancer Cooperative Group. Eur J Cancer 1992;28A(10):1667-1670.

68. Lehnert M, Mross K, Schueller J, et al. Phase II trial of dexverapamil and epirubicin in patients with non-responsive metastatic breast cancer. Br J Cancer 1998;77(7):1155-1163.

69. Neri B, Pacini P, Bartalucci S, et al. Epirubicin high dose therapy in advanced breast cancer: preliminary clinical data. Int J Clin Pharmacol Ther Toxicol 1989;27:388-391.

70. Piccart MJ, Bruning P, Wildiers J, et al. An EORTC pilot study of filgrastim (recombinant human granulocyte colony stimulating factor) as support to a high doseintensive epiadriamycin cyclophosphamide regimen in chemotherapy-naïve patients with locally advanced or metastatic breast cancer. Ann Oncol 1995;6(7):673-677.

71. Jakobsen P, Steiness E, Bastholt L, et al. Multiple-dose pharmacokinetics of epirubicin at four different dose levels: Studies in patients with metastatic breast cancer. Cancer Chemother Pharmacol 1991;28(1):63-68.

72. Bonneterre J et al., Long-term cardiac follow-up in relapse-free patients after six course of fluorouracil, epirubicin, and cyclophosphamide, with either 50 or 100 mg of epirubicin, as adjuvant therapy for node-positive breast cancer: French Adjuvant Study Group. J Clin Onc 2004 (August 1); 22 (15) 3070-3079.

73. [Pr]Pharmaorubicin* RDF[†] (epirubicin hydrochloride injection) Product Monograph. Pfizer Canada Inc, May 5, 2005.

**PART III: CONSUMER INFORMATION**

**Epirubicin Hydrochloride Injection**
**50 mg/vial**
**Sterile**

**This leaflet is part III of a three-part "Product Monograph" published when Epirubicin Hydrochloride for Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Epirubicin Hydrochloride for Injection. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**Epirubicin Hydrochloride for Injection and cancer treatment:**

***What the medication is used for and What it does:***
*Epirubicin Hydrochloride for Injection* is a chemotherapy drug, often used in combination with other drugs to kill cancer cells. Most chemotherapy agents (including *Epirubicin Hydrochloride forInjection*) work by killing rapidly dividing cells, such as cancer cells. This action can affect normal cells as well. *Epirubicin Hydrochloride for Injection* has been used in various kinds of cancer, including lymphoma, ovarian, and breast cancer.

In breast cancer, it can be used following surgery and/or radiation as adjuvant or additional therapy. Here, it is used to kill cancer cells that have 'escaped' the tumor and could spread to other parts of the body (like the bones, liver, or lungs), where the cancer can grow again and recur. If breast cancer has spread to the lymph nodes in the axilla (armpit), there is higher chance of recurrence if no treatment is given. (The axillary lymph nodes normally drain fluid from the breast and arm.) The extent of the cancer cell spreading may be a factor when a chemotherapy regimen is chosen. BEFORE STARTING TREATMENT YOU AND YOUR DOCTOR SHOULD DISCUSS TREATMENT OPTIONS BEST SUITED TO YOU, TAKING INTO CONSIDERATION YOUR CONDITION AND OTHER HEALTH CONCERNS THAT YOU MAY HAVE.

In other cancers, chemotherapy can be used to reduce tumor size,or stop them from growing. Understand why your doctor has chosen the particular chemotherapy regimen to be used, and know all the risk and benefits before starting therapy.

***What is in your medication?***
Your medicine is called Epirubicin Hydrochloride for Injection. Each vial contains 50 mg of the active ingredient, epirubicin hydrochloride, in a freeze-dried powder. It also contains the non-medicinal ingredient lactose.

## WARNING AND PRECAUTIONS

Before using Epirubicin Hydrochloride for Injection, tell your doctor if any of the following applies to you:

- if you have or have experienced a sensitivity or allergic reaction to epirubicin or any other component of the product (see ***what is in your medication***), other anthracyclines or anthracenediones such as doxorubin hydrochloride, daunorubicin hydrochloride, mitoxantrone or mitomycin C.
- if you have low blood cell counts due to a decreased ability of the bone marrow to produce blood cells
- if you have severe liver disease
- if you have a heart disease, recent heart attack or irregular heartbeat
- if you are taking other drugs (including calcium channel blockers) or have been previously treated with Epirubicin Hydrochloride for Injection or other anti-cancer drugs.

## PROPER USE OF THIS MEDICATION

***How is* Epirubicin Hydrochloride for Injection *given?***
Some patients may receive *Epirubicin Hydrochloride for Injection* through a vein in the arm ("intravenously" or "IV") by their doctor or nurse, usually in the hospital, outpatient department or clinic.

If you are getting many injections over several weeks or months, for your convenience, your doctor may insert a catheter (thin tube) or port into a large vein in your body that is placed there as long as it is needed. Medicines get injected through the catheter or port rather than directly into a vein.

***Is treatment with* Epirubicin Hydrochloride for Injection *painful?***
It is unusual to feel pain during the injection, however, if you do feel pain or burning, you should immediately tell your nurse or doctor.

***How much time does it take to get a treatment with* Epirubicin Hydrochloride for Injection*?***
It usually takes about 5 minutes to inject *Epirubicin Hydrochloride for Injection*. However, you may get other medicines before or after *Epirubicin Hydrochloride for Injection*, so your entire treatment may last an hour or longer.

***How long will I need treatment?***
Your doctor will determine the length of your treatment based on your treatment goals, the medicines you receive, and how your body responds to those medicines. Adjuvant chemotherapy for breast cancer usually lasts 3-6 months, however.

Chemotherapy is usually given in cycles that include rest periods between treatments. The rest periods give your body a chance to build healthy new cells and regain your strength before your next treatment. *Epirubicin Hydrochloride for Injection* is given in treatment cycles of 21 days or 28 days. You may receive one dose of *Epirubicin Hydrochloride for Injection* every three or four weeks (on Day 1 of the cycle). Or, you may receive *Epirubicin Hydrochloride for Injection* in two doses - one dose on Day 1 of the cycle, and another dose on Day 8. Your treatment cycle will depend on your medical condition and the other chemotherapy medicines you are getting.

***Will I be able to work?***
Some people work full time, while others work part time or wait until their chemotherapy treatments are finished. It depends on the type of job you have and the side effects you experience.

***Is it okay to become pregnant or nurse a baby?***
No. *Epirubicin Hydrochloride for Injection* can be harmful to an unborn child. If there is any possibility that you may become pregnant, ask your doctor about using birth control to prevent pregnancy during your treatment with *Epirubicin Hydrochloride for Injection*. Tell your doctor right away if you become pregnant during treatment. If you have been nursing, you should stop before starting treatment with *Epirubicin Hydrochloride for Injection*. Ask your baby's doctor to recommend a formula that would be best for your baby.

***What should men consider when taking Epirubicin Hydrochloride Injection?***
Men undergoing treatment with epirubicin should use effective contraceptive methods.

***Your first treatment: what to expect***
**There will be tests**
Before you get your first treatment, your doctor will probably order blood tests to check your blood count (white blood cells, red blood cells, and platelets), heart and liver function tests, X-rays or other tests. These "baseline" tests show your current condition, and will be compared to future test results.

***You may get one or more medicines***
Before your first treatment, you and your doctor will discuss all of the medicines you will receive during the treatment session. In addition to *Epirubicin Hydrochloride for Injection*, you may get other intravenous (IV) medicines, such as a medicine to prevent nausea, and other chemotherapy medicines. You can also ask your doctor about possible side effects and what to do if you experience any of these side effects.

***Receiving your treatment***
If you are getting your treatment at a clinic or a hospital, there is usually a comfortable treatment room where you can relax while you are getting your medicines.

Your nurse may insert a very thin plastic tube (IV) into your vein, which allows fluid to drip into your vein from a plastic bag. If you are getting a medicine to prevent nausea, you will probably take that medicine first. Then you will get the rest of your IV medicines - including Epirubicin Hydrochloride for Injection-one at a time.

***What happens after treatment?***
After you have completed all your chemotherapy treatments, your doctor will check you regularly to make sure the cancer has not returned.

## EFFECTS AND WHAT TO DO ABOUT

***There may be side effects***
Like all medicines, *Epirubicin Hydrochloride for Injection* may cause side effects. Everyone reacts differently to chemotherapy and not all people will experience every side effect. The most common side effects of chemotherapy medicines (including *Epirubicin Hydrochloride for Injection*) are hair loss, increased risk of infection, nausea, vomiting, fatigue, and mouth sores. The kinds of side effects, how often they occur, and how bad they may be could be related to the dose of chemotherapy, or the regimen used.

Another much less common side effect of *Epirubicin Hydrochloride for Injection* that can be serious, and in some cases irreversible, is damage to the heart muscle. This condition can cause symptoms such as shortness of breath, swelling in the ankles, and fluid retention. If you have these symptoms, call your doctor right away. There are medicines to treat this condition.

A small number of patients (less than 1%) may develop secondary leukemia up to 5 years after treatment with *Epirubicin Hydrochloride for Injection*.

The chances of developing heart damage or leukemia appear to be related to either how much chemotherapy you have received, or the dose of *Epirubicin Hydrochloride for Injection* used. Be sure you discuss the risks and benefits of various chemotherapy options with your doctor, and understand the side-effects both immediate and long-term that you could have from your treatment before you start therapy.

*Epirubicin Hydrochloride for Injection* is a red-orange coloured liquid and will make your urine turn red for a few days after treatment.

Don't be alarmed – this is normal!

***All about chemotherapy side effects***
Hearing about all of the side effects from chemotherapy may seem overwhelming. But many people go through chemotherapy with very mild or few side effects.

Other people, who are more sensitive to chemotherapy, may have many side effects - but they can usually be controlled. Everyone reacts in a different way to chemotherapy.

Because *Epirubicin Hydrochloride for Injection* is given with other chemotherapy medicines, it is sometimes hard to know which medicine is causing a particular side effect. If you are having a problem with side effects, call your doctor or nurse. They can suggest medicines or other ways to prevent or relieve your discomfort. Do not skip doses or make changes in your treatment on your own.

***Why do side effects occur?***
Chemotherapy medicines work by killing the fastest growing cells in the body, which include cancer cells and some normal cells. Normal cells that grow very rapidly are in your bone marrow, lining of the mouth, stomach, and hair follicles. These fast-growing cells can be affected by the chemotherapy medicines too, sometimes causing side effects such as low white blood cell count, low red blood cell count (anemia), nausea and vomiting, mouth sores, rash, itch and hair loss. These side effects usually disappear after treatment ends. Before your next cycle of chemotherapy, your white blood cells count normally increases and new cells grow back. After your chemotherapy is completely finished, your hair will begin to grow back.

SIDE EFFECTS YOU MAY EXPERIENCE WITH CHEMOTHERAPY

***Hair loss***
Hair loss is common in chemotherapy with *Epirubicin Hydrochloride for Injection*. However, the hair loss is temporary, and your hair usually starts to grow back within 2 or 3 months after you've finished your treatments.

Many breast cancer survivors suggest getting a wig before you start chemotherapy treatment. That way, your stylist can match your current hair colour and set it in the same style. While wigs can be expensive, there are organizations such as The Canadian Cancer Society that provide wigs free of charge. In addition to wigs, some women like to wear stylish hats, scarves or turbans to cover their head.

***Infection***
A week or two after a chemotherapy cycle, your white blood cell count may be low. This is the most dangerous time for getting an infection. White blood cells defend your body against infections. When there are very few white blood cells, there may not be enough to fight off an infection. It's important to know the signs of infection so that you can get treatment before the infection becomes serious. The signs of infection include:

- fever over 38°C (100°F),
- chills or sweating,
- sore throat or coughing,
- redness or swelling around a cut, wound or a catheter site,
- a burning feeling when you urinate,
- unusual vaginal itching or discharge.

Your doctor may prescribe oral antibiotics to help prevent infection during chemotherapy. Your doctor may also give you a medicine to help increase the number of your white blood cells. If there is evidence of an infection, your doctor may need to admit you to the hospital for a short period of time to receive intravenous antibiotics.

*If you have signs of an infection, call your doctor right away. Waiting too long (even a few hours) can lead to a serious illness.*

**The following tips can help you prevent infections.**
- Wash your hands often. Use lotion afterwards to prevent your skin from becoming dry and cracked.
- Bathe or shower every 1 to 2 days.
- Be careful not to cut yourself when you use a knife, scissors, razor or other sharp objects.
- Stay away from people who are sick.
- Have someone else clean cat litter boxes, bird cages or fish tanks.
- Eat well-balanced meals.

***Nausea and vomiting***
The amount of nausea and vomiting varies widely from person to person. Some have mild nausea and vomiting, while others may have severe nausea and vomiting for a short time after treatment. Nausea and vomiting may start right after a chemotherapy treatment or several hours later. Your doctor can give you medicine to prevent nausea or reduce its severity. If you've been treated with a medicine for nausea, but still feel sick to your stomach or you vomit, tell your doctor. There are other medicines your doctor can give you that may work better for you. You can also try drinking clear fluids (water, diluted soft drinks, apple juice, and broth) or sucking on popsicles and ice chips. Here are some tips that may help reduce nausea.

- Eat small meals or snacks throughout the day instead of 2 or 3 large meals.
- Eat foods that are cold or at room temperature.
- Cut out foods that are fried, spicy, fatty or sweet.
- Stay away from odours that may bother you such as cooking smells, cigarette smoke, car exhaust or perfume.
- Sit upright in a chair after eating - don't lie flat for at least 2 hours.
- Wear loose-fitting clothes, especially around the waist.
- Suck on ice, mints or sour candy (but avoid sour candy if you have mouth sores).
- Eat something light a few hours before your chemotherapy treatment.

***Fatigue***
Feeling tired - or fatigued - is one of the most common side effects of chemotherapy. Many other factors such as stress, diet, sleeping patterns, and your age can also cause fatigue. For some, fatigue may start to improve 2 to 3 months after you complete your chemotherapy treatments. Here's how you can help reduce fatigue.

- Plan your activities. Allow rest between periods of activity. List all of the things you have to do, and number them in order of importance. Only do the things on your list that must get done. Leave the other tasks for another day.
- Ask family and friends to help you with driving, housework or other tasks. For example, ask your friend to pick up a few things for you the next time she goes to the supermarket.
- Eat a well-balanced diet.
- Do light exercise regularly.

***Anemia***
Chemotherapy medicines affect the bone marrow, which is where red blood cells are formed. Red blood cells carry oxygen to the muscles and other tissues in your body. When there are too few red blood cells, your muscles, and other body tissues can't get enough oxygen to do their work, and you feel exhausted. If your red blood cell count drops very low, you may also feel weak or dizzy, or may have shortness of breath. These are all symptoms of anemia. If you have these symptoms, tell your doctor or nurse. Your doctor may give you medicine to treat anemia that is caused by chemotherapy. Do not start taking iron tablets on your own - they may not work for anemia caused by chemotherapy medicines and can make your nausea worse.

***Mouth sores***
Chemotherapy medicines may cause sores in your mouth and throat about a week or two after a chemotherapy treatment. It's important to keep your mouth clean during the time you're having chemotherapy because mouth sores can be a source of infection. Be sure to brush your teeth after each meal with a soft toothbrush. You should also see your dentist before you start chemotherapy to have your teeth cleaned and to take care of any dental work you might need. Mouth sores can be painful, but there are a few things you can do to relieve the pain and prevent further irritation.

- Talk to your doctor about medicines you can use to relieve painful mouth sores. There are anesthetic lozenges and sprays you can use to numb the sores before you eat.
- Eat your food cold or at room temperature. Eating warm or hot food can irritate your mouth sores.
- Cook your food until it's soft and tender.
- Eat soft, smooth foods such as applesauce, bananas, cooked cereals, scrambled eggs, yogurt, noodles, macaroni and cheese, mashed potatoes, cottage cheese, custards, puddings, milk shakes, and ice cream. You can also make foods smoother and easier to eat by pureeing them in a blender. Some people enjoy eating baby food as the pureed fruits are tasty, easy to store, and ready to eat.
- Cut out spicy or acidic foods (citrus fruits or tomatoes) or rough, coarse foods that can irritate mouth sores such as toast and raw vegetables.
- Use a straw to drink liquids. Rinse your mouth with water to remove pieces of food that may get stuck in the mouth sore.
- Avoid mouthwashes that contain alcohol, smoking cigarettes or drinking alcoholic beverages (beer, wine, and hard liquor).

***Menstrual changes***
Chemotherapy reduces the hormone production of your ovaries. Some pre-menopausal women may experience irregular menstrual periods, while others may stop menstruating completely. These changes can be temporary or permanent (menopause); it varies from woman to woman. In addition to these, other menopause type symptoms may also occur, such as hot flashes, irritability, or vaginal dryness, itching or burning. Try using a water-based vaginal lubricant or moisturizer for vaginal dryness, or consult your doctor.

**When to call your doctor's office**
***Call your doctor or nurse if you:***
- have a fever over 38ºC or other signs of infection,
- have shortness of breath along with fluid build-up (for example, swelling in the ankles),
- vomit for more than 24 hours, or you are still having nausea or vomiting although you've taken medicine to control it,
- have symptoms of dehydration-your skin may appear flushed, dry, and pale; you may not urinate very much; you may feel irritable or confused. If you are having diarrhea or are vomiting often, you may become dehydrated.
- bleed or bruise easily,
- have a new skin rash or itching,
- have pain where *Epirubicin Hydrochloride for Injection* was injected,
- suspect that you are pregnant.

***This is not a complete list of side effects. For any unexpected effects while taking Epirubicin Hydrochloride for Injection, contact your doctor or pharmacist.***

**REPORTING SUSPECTED SIDE EFFECTS**
**To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:**

**toll-free telephone: 866-234-2345**
**toll-free fax: 866-678-6789**
**By email: cadrmp@hc-sc.gc.ca**

**By regular mail:**
**National AR Centre**
**Marketed Health Products Safety and Effectiveness Information Division**
**Marketed Health Products Directorate**
**Tunney's Pasture, AL 0701C**
**Ottawa ON K1A 0K9**

***NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Hospira Healthcare Corporation. at: 1-866-488-6088, Option 4.

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